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**SECULAR CHANGES IN CLINICAL FEATURES AT PRESENTATION OF RHEUMATOID ARTHRITIS: INCREASE IN COMORBIDITY BUT IMPROVED INFLAMMATORY STATES**

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EN, SN, LC, JD, DAW, PK and AY have no conflicts of interest to declare.

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**Abstract**

**Objective:** To examine secular trends in demographic, clinical manifestations and comorbidity on first presentation of RA prior to DMARD treatment.

**Methods:** 2701 patients were recruited over 25 years to two UK-based RA inception cohorts: the Early RA Study (9 centres; 1986-2001) and the Early RA Network (23 centres; 2002-2012). Trends in demographic and baseline clinical/laboratory and radiographic variables and comorbidities were estimated using mixed effects models, including random effects for recruitment centre.

**Results:** Age-at-onset increased from 53.2 to 57.7 years in 1990 and 2010 respectively (2.6 months/year; 95% CI 1.2-4.1). Gender-ratio, the proportion living in deprived areas and smoking status were unchanged ( $p > 0.05$ ) and there were no changes in the proportion seropositive or erosive at baseline ( $p > 0.05$ ). After controlling for treatment at the time of assessment, ESR reduced and haemoglobin increased over time ( $p < 0.05$ ), however HAQ, DAS, DAS28, and joint counts were unchanged ( $p > 0.05$ ). The overall prevalence of comorbidity increased from 29.0% in 1990 to 50.7% in 2010, mainly due to cardiovascular and non-cardiac vascular conditions including hypertension. There was a significant increase in BMI (0.15 units/year; 95% CI 0.11-0.18), resulting in an increase in the prevalence of obesity from 13.3% in 1990 to 33.6% in 2010.

**Conclusions:** Age-at-onset and comorbidity burden, especially obesity have increased at RA presentation over 25 years, reflecting wider demographic trends at the population level. In contrast there were no accompanying changes in disease severity assessed by composite markers of disease activity, radiographic erosions, seropositivity or HAQ at presentation. Treatment strategies in early RA should take greater account of the impact of co-morbidity on outcomes.

**SIGNIFICANCE AND INNOVATIONS**

- Increasing age and level of comorbidity were observed at presentation of rheumatoid arthritis (RA) over a 25 year period.
- In contrast, RA disease severity remained stable over time, prior to disease-modifying treatment.
- Modern management of RA should incorporate a detailed assessment of comorbidities in order to better inform treatment stratification.

The need to better understand patterns of disease expression in rheumatoid arthritis (RA) and also wider patient characteristics is well recognised in modern day rheumatology practice and stratified medicine. Several studies report a decreasing severity of RA over time, though some controversy remains (1–4)(5). Reports on long-term outcomes of disease (6–10), attribute the reduction in RA severity mainly to the use of earlier and more intensive disease modifying treatments (11). These data are compromised by the majority of studies not allowing for an assessment of disease severity on first presentation, prior to disease-modifying anti-rheumatic drug (DMARD) therapy or long term steroids, due to the nature of the data collected. As a result, trends at presentation may be confounded by treatment commencement prior to the completion of disease severity assessments. Furthermore, there is very little data on the presence of comorbidities in early RA, although these have an influence on treatment efficacy and disease outcomes. An important reason for this is failure or variation in the capture of this information.

Ascertaining the burden of comorbidities in RA is important in clinical practice for several reasons, and requires an incorporation of strategies to manage these from the time the patient first presents, as well as suppressing the inflammatory burden of RA with traditional DMARDs. This is exemplified by the well recognised independent influence of RA on adverse cardiovascular outcomes (12). Furthermore, the impact that comorbidities can have on DMARD and biologic tolerability and efficacy requires careful treatment selection, to optimise outcomes. Thus the treatment strategy selected at first presentation of RA should be reflective of the index condition as well as all other co existing factors.

An increased prevalence of obesity and conditions such as diabetes have been reported in the general population (13,14) but, with one exception, not specifically in RA (1). The primary objective of this study was therefore to determine whether demographic, clinical characteristics and the presence of comorbidities at RA presentation, prior to the initiation of

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DMARD therapy, have changed over the past 25 years. The study uses data from two consecutive UK inception cohorts and hypothesizes that (i) in line with a reduced incidence, age at symptom onset would have increased; (ii) due to wider societal trends and increasing age at onset, obesity and the presence of comorbidities will have increased; and (iii) based on previous literature, and due to better general population health (e.g. greater awareness of the effects of smoking) disease severity as indicated by clinical characteristics, inflammatory markers and symptoms would have decreased.

**METHODS*****Patient Databases***

The Early RA Study (ERAS) and Early RA Network (ERAN) are multi-centre inception cohorts of early RA, which recruited from 9 rheumatology centres in England between 1986-2001, and 23 centres in England, Wales and Ireland from 2002-2012, respectively, as previously described in detail (10). Recruitment figures and median follow up for ERAS and ERAN were 1465 and 10 years (maximum 25 years), and 1236 and 6 years (maximum 10 years) respectively. ERAS and ERAN are consecutive studies with similar design and patients recruited within the first 2 and 3 years from symptom onset respectively and prior to DMARD therapy in ERAS and the greatest majority of ERAN.

***Clinical, laboratory and radiographic variables***

Standard demographic, clinical and laboratory variables were recorded at the time of patient visit ("baseline" visit) and yearly thereafter and strictly prior to DMARD use in ERAS, although in ERAN a small proportion of patients were recruited after DMARD initiation (indicated on the database). Variables recorded in both cohorts included gender, age at disease-onset, recruitment year, baseline rheumatoid factor and/or anti-CCP, haemoglobin,

ESR and Health Assessment Questionnaire disability index (HAQ).(15) Individuals in both cohorts were classed as living in a deprived area based on their postal code being ranked in the lowest quintile of areas in England by Index of Multiple Deprivation 2007. There were some differences in the recording of certain variables relating to disease activity between ERAS and ERAN, namely in the recording of the tender and swollen joint count variables (TJC, SJC), and patient global assessment (PGA). In ERAS, disease activity was calculated based on the original three variable Disease Activity Score (DAS(16,17)), whereas in ERAN the four-variable DAS28 ESR method was used(18–20). In line with the change to the DAS28 score, joint counts changed from being out of 44 joints to 28 and the focus of PGA changed from pain to disease activity, respectively. A formula was used to convert the ERAS DAS scores to DAS28 scores (21) to make them comparable across both cohorts, though since they are not interchangeable they were examined separately in the two cohorts. Data on comorbidities and extra-articular manifestations were recorded at every visit in the medical notes and on the case reporting forms, the comorbidities subsequently coded based on the ICD-10 coding system. These codes were used to generate a numeric count from which the weighted Charlson Comorbidity Index (CCI (21)) was generated. Since RA is the index condition for this study it was excluded from the CCI score (modified CCI).

### ***Treatment profiles***

All centres followed the framework of published UK guidelines for management of RA although treatment choice was ultimately left at the discretion of the treating clinician(10). In ERAN, a small proportion of patients used synthetic DMARDs prior to recruitment into the study. Steroid use in primary care prior to rheumatology review was recorded where available. Non-steroidal anti-inflammatory drug (NSAID) use was not recorded and was therefore not included in the analysis.

### ***Statistical Analysis***

Mixed effects models, accounting for clustering of patients within centres with a random effect, were used to estimate the annual change in demographic and clinical variables at first presentation to the rheumatologist. The demographic or clinical variable was entered into separate models as the outcome and calendar year of onset included as a predictor. Linear models were used for continuous variables, and logistic models for binary variables. All analyses were undertaken in Stata 12.1. For variables that were identical across both cohorts (e.g. age at onset, sex, ESR), linear trends over time were compared to non-linear trends estimated using restricted cubic splines (knots at 1990, 1995, 2000 and 2005), and piecewise models with linear trends estimated separately within each cohort. Based on visual inspection of the estimated trends and the comparison of model fit using Bayesian Information Criterion (BIC), trends over time for all variables were adequately approximated by a linear function. Therefore only linear trends are displayed in the results. Note that for logistic models estimates of prevalence are curvilinear due to transformation from the logit scale. Standard errors for all models were estimated using bootstrap approach with 1000 resamples. Trends in baseline demographic variables were adjusted for age, sex, and the time between symptom onset and baseline visit. Trends in clinical variables were adjusted for age, sex and use of steroids or disease modifying treatment prior to the baseline visit. ESR was log transformed for analysis and then back transformed for display.

## **RESULTS**

### ***Trends in demographic variables***

Demographic and clinical characteristics by cohort are given in Table 1. The estimated trends for variables that were assessed in the same manner across both cohorts are shown in Figure 1. Age at symptom onset increased from 53.2 years in 1990 to 57.7 years in 2010, an increase



of 2.6 months per year ( $b=0.22$  years/year; 95% CI 0.10 to 0.34). The proportion of patients that were female, living in a socially deprived area, and were current smokers did not change significantly over the 25-year period of recruitment to the two cohorts ( $p>0.05$ ).

**Figure 1.** Trends in demographic variables and clinical characteristics.

### ***Overall comorbidity burden***

Table 2 shows the overall comorbidity burden by type of comorbidity at baseline across both cohorts. The main conditions reported were non-cardiac vascular, mainly hypertension, followed by endocrine disease (mainly thyroid problems), cardiovascular (mainly ischaemic heart disease) and respiratory diseases (mainly COPD and asthma). Diabetes was reported in 2.0% ( $n=54$ ) and osteoporosis in 1.3% at baseline ( $n=34$ ; 13 in ERAS, 21 in ERAN).

Psychiatric comorbidity represented 3% of comorbidities at baseline, including depression and anxiety ( $n=68$ ) and less commonly, anorexia and psychosomatic disease ( $n=13$ ).

Extra-articular RA disease was present in 12% of patients at baseline and included rheumatoid nodules, pulmonary interstitial lung disease (ILD) and secondary Sjogren's. ILD in particular was reported in 0.7% ( $n=18$ ; 5 in ERAS, 13 in ERAN).

### ***Trends in comorbidities***

Trends in comorbidities over time are shown in Figure 2 with further information in the supplementary material. Presence of a comorbid medical condition increased substantially with time, from 29.0% in 1990 to 50.7% in 2010. Relating to a 5% increase in the odds of prevalent comorbidity per year later onset, across the observed period (OR=1.05; 95% CI 1.03 to 1.07). Similar relative increases in the presence of CCI (modified CCI excluding RA) (9.6% to 19.8%; OR=1.04; 95% CI 1.02 to 1.07), cardiovascular conditions (1.9% to 6.8%; OR=1.07; 95% CI 1.03 to 1.11) and non-cardiac vascular conditions (3.6% to 30.4%; OR=1.13; 95% CI 1.10 to 1.16) including hypertension were observed. There was a

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considerable increase in BMI over time ( $b=0.15$ ; 95% CI 0.11 to 0.18). This related to an increase in the prevalence of obesity from 13.3% in 1990 to 33.6% in 2010 (OR=1.06; 95% CI 1.04 to 1.08). The presence of extra-articular conditions (mainly nodules, Raynaud's and Sjogren's) reduced slightly though non-significantly. Small but non-significant increases were observed for diabetes (1990: 1.3%; 2010: 2.5%; OR=1.04; 95% CI 0.99 to 1.08), respiratory conditions (1990: 4.5%; 2010: 5.6%; OR=1.01; 95% CI 0.99 to 1.04) and gastrointestinal conditions (1990: 2.3%; 2010: 2.7%; OR=1.01; 95% CI 0.97 to 1.05). Trends in other conditions including interstitial lung disease and vasculitis are not displayed due to low prevalence at baseline.

**Figure 2. Trends in comorbidities over time.*****Trends in disease severity***

Trends in disease severity, adjusting for age at disease-onset, sex, symptom duration and treatment prior to the baseline assessment, are shown in Figure 3. (see supplementary material for unadjusted trends). Controlling for age at disease-onset, sex, symptom duration and treatment prior to the baseline assessment, there was a reduction in baseline ESR (logarithmic scale:  $b=-0.02$ ; 95% CI -0.02 to -0.01) and an increase in haemoglobin ( $b=0.04$ ; 95% CI 0.03 to 0.05). However, controlling for the same variables, HAQ did not change over the period of observation ( $b=0.00$ ; 95% CI -0.01 to 0.01).

**Figure 3. Trends in disease severity.**

Figure 4 displays the estimated trends within each cohort for variables assessed in different ways across the two cohorts. DAS28, TJC and SJC were assessed differently in each cohort. In ERAS DAS28 converted from the original three variable DAS with 44 joint counts did not change significantly over time (DAS28:  $b=-0.01$ ; 95% CI -0.03 to 0.01; SJC44:  $b=0.06$ ; 95% CI 0.09 to 0.20; TJC44:  $b=-0.01$ ; 95% CI -0.16 to 0.13). Similarly, in ERAN the DAS28 and

swollen and tender joints counts did not change significantly over time (DAS28:  $b=-0.01$ ; 95% CI -0.09 to 0.06; SJC28:  $b=-0.15$ ; 95% CI -0.048 to 0.18; TJC28:  $b=-0.18$ ; 95% CI -0.50 to 0.14).

**Figure 4.** Trends of variables assessed in different ways across ERAS and ERAN (swollen & tender joints recorded out of 44 in ERAS and 28 in ERAN).

### *Sensitivity analysis*

Although the trends in disease variables reported above were adjusted for treatment at baseline, a further sensitivity analysis was undertaken to examine whether earlier treatment explained the lower levels of inflammation. Excluding individuals prescribed steroid or DMARDs prior to the baseline assessment, the trends for ESR (logarithmic scale:  $b=-0.02$ ; 95% CI -0.03 to -0.02) and Hb ( $b=0.03$ , 95% CI -0.02 to -0.04) remained significant.

## **DISCUSSION**

This study provides insights into the changing circumstances of the first presentation of RA over 25-years, which may have important clinical and health economic implications, for example, on the screening and management of comorbid diseases, treatment stratification and resource allocation. The detailed analysis of patient and disease characteristics and comorbidities at RA presentation, prior to DMARD use and controlling for the small number of patients who received steroids prior to study entry, demonstrates: 1) an increasing age at symptom onset 2) increasing comorbidity burden 3) reduced inflammatory states and unchanged patient symptoms and measures of disease activity.

The prevalence of comorbid conditions on presentation of RA has significantly increased over twenty-five years with rising levels of cardiovascular and non-cardiac vascular morbidity (including hypertension) as well as the overall CCI. Our findings are in line with the considerable changes in population demography seen in the UK over time, with a rising

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prevalence of multimorbidity (22), and obesity (23). The obesity 'epidemic' has been a highly researched topic across the world, with a recent review supporting increasing levels of obesity (24), all of which has wider public health relevance. A possible explanation for this change, aside from it representing a true increase in certain comorbidities, is an increased awareness of certain conditions over time and better diagnostic and reporting modalities. Although non-significant, there was also an increasing trend in endocrine, respiratory and gastrointestinal conditions at baseline.

Whether these observed changes in comorbidity represent a real increase in conditions or are alternatively due to improved recognition, the fact is that the recognized burden of comorbidity has increased and as such this should impact on modern rheumatology management. The increase in conditions including obesity, hypertension, ischaemic heart disease and anxiety/depression at RA presentation make it increasingly important that early assessment of new cases includes a broad clinical assessment. Each of these co morbid conditions carries a health burden, worthy of treatment and amelioration. Similarly, diabetes, osteoporosis and extra-articular ILD, although less common at baseline, are associated with significant morbidity and should be screened at baseline.

Aside from their direct impact on disease outcomes, comorbidities influence the choice of pharmacotherapy, for example steroid use in patients with diabetes, osteoporosis and obesity; interstitial lung disease and use of methotrexate, leflunomide or TNF inhibitors; gastrointestinal disease and use of non-steroidal anti-inflammatory drugs. Therefore, the emphasis at first presentation of RA should not just be on the index disease (RA) but also on other co-existing conditions. Treat-to-target strategies are now widely accepted as best clinical practice resulting in better outcomes. Emerging evidence, however, demonstrates that multimorbidity negatively impacts treatment of RA to target, with lower achievement of disease remission in multimorbid patients(22–24)(25)(26). Reasons for this include concerns

regarding treatment intensification in the presence of multiple co-existing conditions. Whilst treatment-intensification should still remain a priority in poorly controlled disease, it is inevitable that in the presence of comorbidity, this will need to be carefully considered and tailored to the individual patient. However, despite existing national and international guidelines on the importance of taking into account comorbidities (27), there is little guidance on how to best manage these patients.

We propose that clinicians in busy clinical settings should screen for comorbidity, at the very least for the specific conditions we have identified in this report, based on their frequency, potential impact on RA outcome and the availability of relative simple screening tools, with care plans in place for rapid referral to other specialists as necessary. The negative influence on outcome conferred by a delay in initiating DMARDs, which did not improve over the course of the 25-year study period, versus the potential use of suboptimal treatment combinations because of the presence of comorbidity is an important issue that clinicians should be aware of, with respect to both short and long-term disease outcomes.

It is interesting that whilst comorbidities are increasing at disease-onset, they are accompanied by an unchanged RA severity. The improvement in ESR observed over time somewhat contradicts the significant increase in BMI and obesity, as these contribute to a higher inflammatory load. However the significant rise in haemoglobin may in part explain the fall in ESR.

The later onset age of RA observed in this study may indicate decreasing RA incidence. This is supported by previous studies showing similar trends (20, 21) and suggesting a birth cohort effect, that is, a decreasing likelihood of developing RA with successive generations. An alternative explanation could be a gradual lowering of the clinical threshold for diagnosing RA in older people, pointing towards a period effect rather than a cohort effect. This explanation is less likely because our results show a shift in the entire age distribution (with

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standard deviations remaining unchanged) and the level of clinical variables remains largely unchanged. Another explanation relates to diagnostic criteria but there is no suggestion that the proportion of people fulfilling criteria for a diagnosis for RA has changed over time. No gender differences were seen over time, similar to other studies (13) and there was no significant change in the proportion of people living in socially deprived areas at the time of recruitment.

Evidence based on longitudinal observational studies, including this study, is important and provides real-life data as opposed to clinical trial data, which include stringent inclusions and exclusion criteria that often exclude patients with multimorbidity. However, this study demonstrates that the burden of comorbidity is high and is increasing over time, at the onset of disease and prior to DMARD use. Data from other studies including the Norfolk Arthritis Register (NOAR), that attempt to account for treatment, add to the ambiguity of the findings in this field (4). Extra-articular manifestations of RA were collected routinely in ERAS and ERAN, some of which are features of established, poorly controlled disease. Despite small numbers at disease onset, there was a trend towards a reduction, but this was non-significant.

The real life setting of the ERAS and ERAN cohorts, the large patient numbers and long patient follow-up covering a quarter of a century are important strengths of this study.

Furthermore, the recruitment of patients within the first 3 years of disease and the availability of information on medical treatments, add to the value of the study and enable the examination of disease presentation prior to external influences, importantly disease-modifying treatments. Limitations of the study include the drop off in numbers of patient recruitment as ERAS wound down and ERAN started, which could have introduced some bias to the results. However, sensitivity analysis using piecewise models and models allowing

for non-linear trends with restricted cubic splines showed no issue with this and trends were estimated treating year of onset as a continuous variable to avoid problems with precision.

Furthermore, assessment of steroid use in primary care may be underestimated and other treatment use that may impact on inflammation, particularly NSAIDs but potentially also statins was not known. This may partially explain the trends for reduced inflammation.

A further limitation relates to the self-reported nature of comorbidities, which may have led to under estimation of the prevalence. For example, the prevalence of depression was lower than expected. We observed a prevalence of 3% for all psychiatric comorbidities which is considerably lower than the estimated prevalence of 17% for depressive disorder alone.

(28) Furthermore, previous research using the ERAS cohort has shown that the prevalence of self-reported clinical depression is far lower than expected in comparison to using a screening tool. (29)

In summary, this study demonstrates rising levels of comorbid conditions on first presentation of RA, especially obesity, and along with the older age at disease-onset, highlights the need for more comprehensive packages of care required at these early stages.

Our findings support intensification of screening for, and addressing of risk factors for comorbidities as part of the overall management of RA in order to improve responses to treatment and improved patient outcomes. We also found decreasing levels of inflammation on presentation of RA whereas other disease activity features and patient symptoms have remained largely unchanged.

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Table 1. Demographic and clinical characteristics at baseline visit

Variable	Values	ERAS (N=1465)			ERAN (N=1236)		
Year of onset	<i>n</i> <sub>missing</sub> , Median (IQR)	0	1992	(3.0)	0	2006	(3.0)
Age at onset	<i>n</i> <sub>missing</sub> , Mean (SD)	0	55.3	(14.6)	0	57.0	(14.2)
Female	<i>n</i> <sub>missing</sub> , <i>n</i> (%)	0	973	(66.4%)	0	839	(67.9%)
BMI	<i>n</i> <sub>missing</sub> , Mean (SD)	199	25.6	(4.5)	117	27.6	(5.3)
Obese	<i>n</i> <sub>missing</sub> , <i>n</i> (%)	199	187	(14.8%)	142	303	(27.7%)
Socially deprived area	<i>n</i> <sub>missing</sub> , <i>n</i> (%)	83	259	(18.7%)	343	143	(16.0%)
Smoker	<i>n</i> <sub>missing</sub> , <i>n</i> (%)	558	199	(21.9%)	19	310	(25.5%)
Comorbidity	<i>n</i> <sub>missing</sub> , <i>n</i> (%)	0	431	(29.4%)	0	653	(52.8%)
Symptoms duration (months)	<i>n</i> <sub>missing</sub> , Median (IQR)	0	6	(7.0)	91	6	(9.0)
HAQ	<i>n</i> <sub>missing</sub> , Median (IQR)	5	1.0	(1.3)	37	1.0	(1.1)
ESR (mmHg)	<i>n</i> <sub>missing</sub> , Median (IQR)	7	37	(3)	183	25	(3)
Haemoglobin	<i>n</i> <sub>missing</sub> , Mean (SD)	5	12.6	(1.6)	32	13.1	(1.4)
DAS	<i>n</i> <sub>missing</sub> , Mean (SD)	13	5.0	(1.2)	46	4.5	(1.6)
TJC	<i>n</i> <sub>missing</sub> , Median (IQR)	5	10	(12.0)	6	5	(9.0)
SJC	<i>n</i> <sub>missing</sub> , Median (IQR)	3	15	(19.0)	5	4	(8.0)
RF and/or Anti-CCP positive	<i>n</i> <sub>missing</sub> , <i>n</i> (%)	9	914	(62.8%)	179	639	(60.5%)
Erosions	<i>n</i> <sub>missing</sub> , <i>n</i> (%)	32	368	(25.7%)	114	330	(29.4%)
Steroid prior presentation	<i>n</i> <sub>missing</sub> , <i>n</i> (%)	0	0	(0.0%)	0	125	(10.1%)
DMARD prior presentation	<i>n</i> <sub>missing</sub> , <i>n</i> (%)	0	0	(0.0%)	0	168	(13.6%)

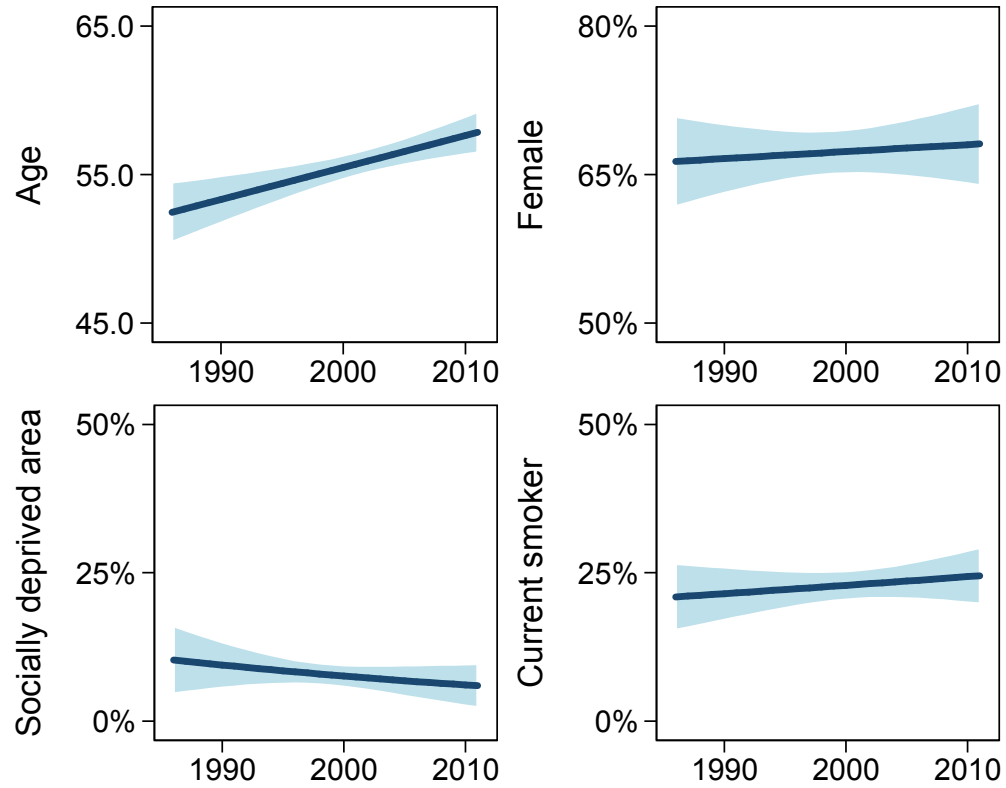
Note: BMI= body mass index; obesity defined as BMI>30; smoker indicates current/previous smoking history; HAQ= Health Assessment

Questionnaire; ESR= erythrocyte sedimentation rate; TJC = tender joint count (out of 44 in ERAS and 28 in ERAN); SJC = swollen joint count (out of 44 in ERAS and 28 in ERAN); PGA = patient global assessment (pain in ERAS and disease activity in ERAN); steroid/DMARD 'prior' indicates use of these drugs prior to enrolment into the study.

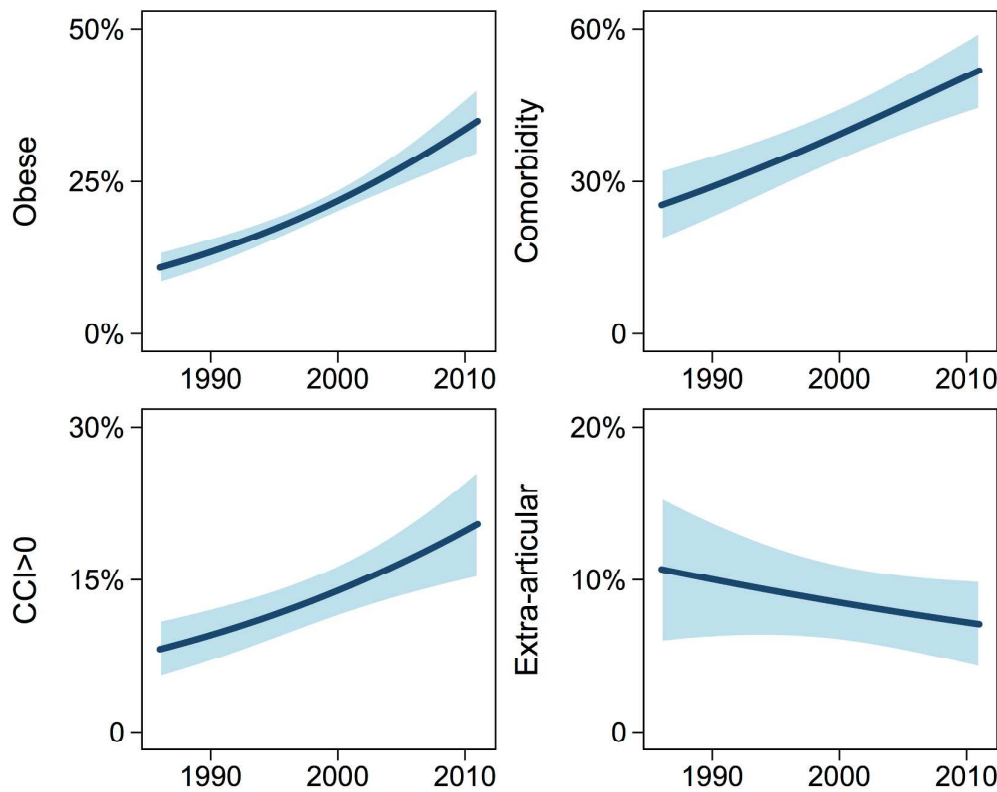
**Table 2.** Comorbidity burden and extra-articular manifestations across ERAS and ERAN on presentation

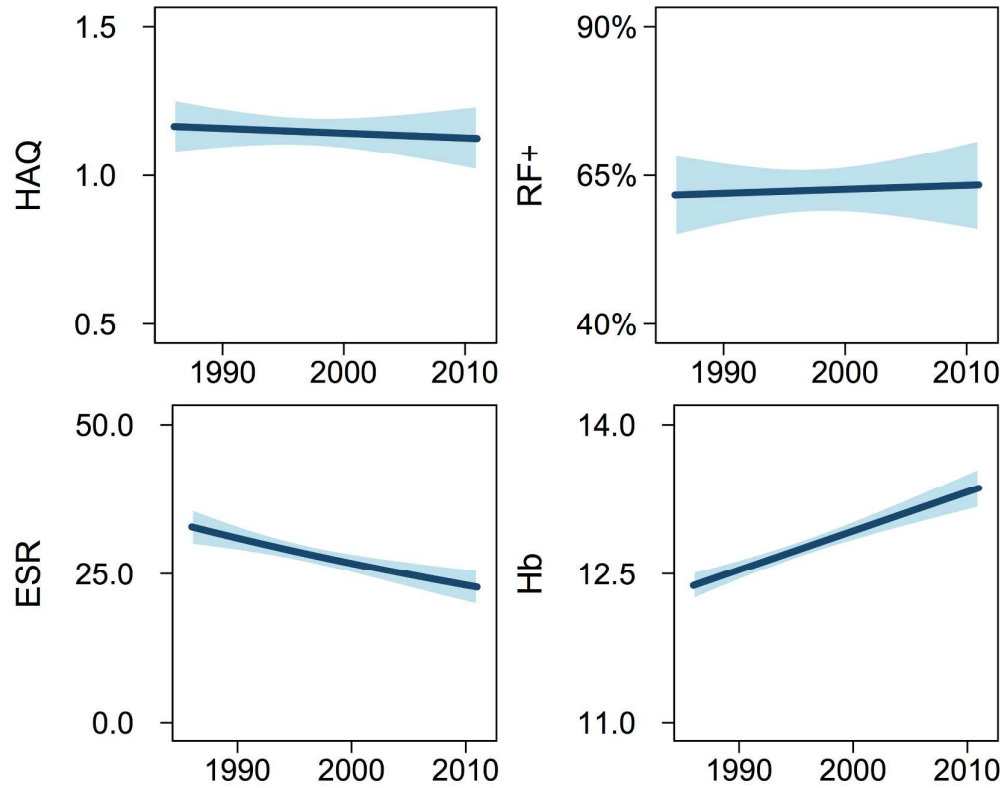
Type of condition	Baseline (n,%)
<b>COMORBIDITIES</b>	
<b>Non-cardiac vascular</b> (e.g. hypertension, peripheral vascular disease)	404, 15
<b>Endocrine</b> (e.g. diabetes, thyroid disease)	253, 9.4
<b>Cardiovascular</b> (e.g. ischaemic heart disease, congestive cardiac failure)	173, 6.4
<b>Respiratory</b> (e.g. COPD, asthma)	141, 5.2
<b>Osteoarthritis</b> (primary or secondary)	124, 4.6
<b>Psychiatric</b> (e.g. anxiety, depression, psychotic illness, anorexia)	81, 3.0
<b>Gastrointestinal</b> (e.g. gastritis, inflammatory bowel disease, diverticulitis)	79, 2.9
<b>Solid cancer</b> (organ-based cancer e.g. lung, prostate)	79, 2.9
<b>Dermatological</b> (e.g. psoriasis, eczema)	70, 2.6
<b>Spinal</b> (e.g. disc disease, spinal stenosis)	51, 1.9
<b>Cerebrovascular</b> (e.g. ischaemic/haemorrhagic stroke)	40, 1.5
<b>Neurological</b>	36, 1.3

<i>(e.g. Parkinson's disease, myasthenia gravis)</i>	
<b>Renal</b>	28, 1.0
<i>(e.g. chronic kidney disease, renal calculi)</i>	
<b>Haematological</b>	24, 0.9
<i>(e.g. anaemia)</i>	
<b>Ophthalmological</b>	25, 0.9
<i>(e.g. cataract formation)</i>	
<b>Gynaecological</b>	16, 0.6
<i>(e.g. non-malignant ovarian or uterine disease)</i>	
<b>Hepatic</b>	7, 0.3
<i>(e.g. alcoholic liver disease)</i>	
<b>Haematological malignancy</b>	4, 0.1
<i>(e.g. leukaemia, lymphoma)</i>	
<b>EXTRA-ARTICULAR MANIFESTATIONS</b>	
<b>All</b>	323, 12
<i>(major, e.g. vasculitis, ILD; minor, e.g. nodules, peripheral nerve entrapment )</i>	



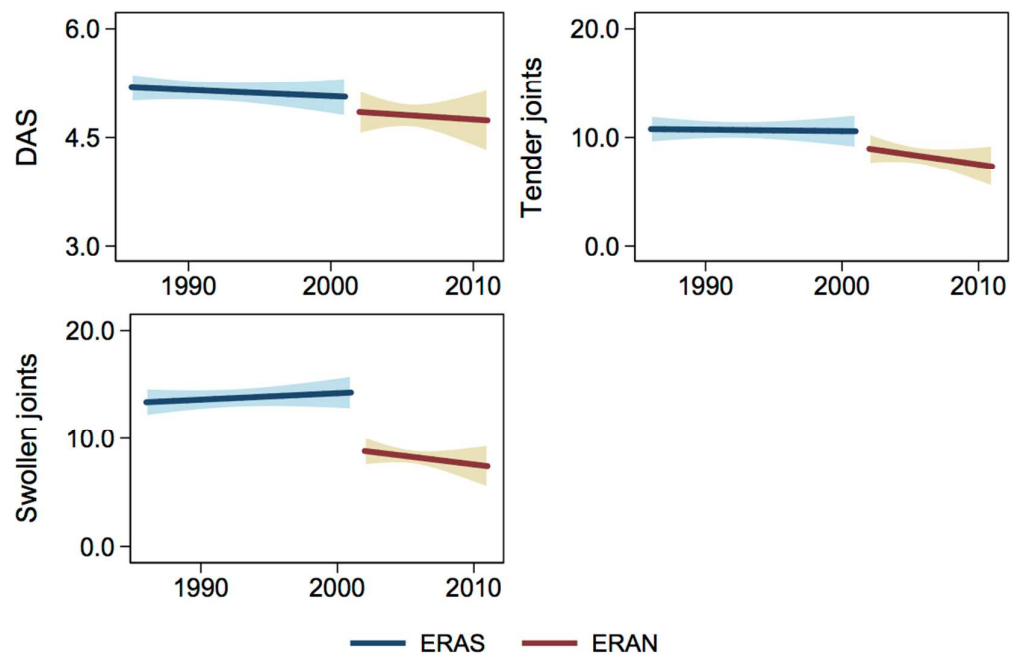
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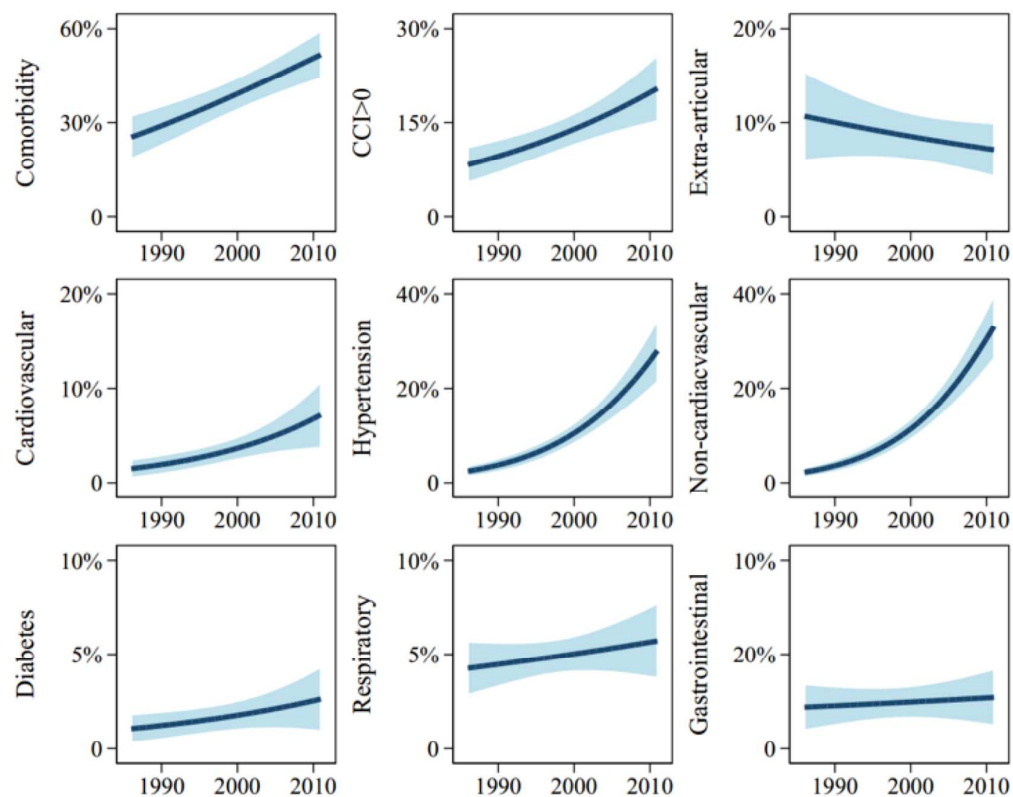
## SECULAR CHANGES IN CLINICAL FEATURES AT PRESENTATION OF RHEUMATOID ARTHRITIS: INCREASE IN COMORBIDITY BUT IMPROVED INFLAMMATORY STATES

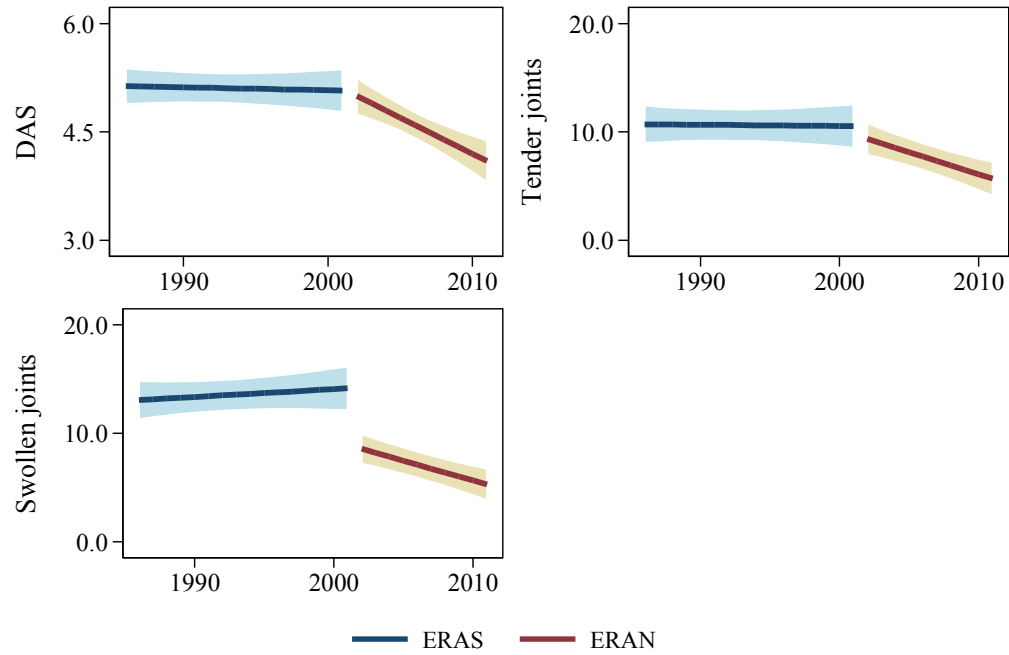
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Figure a shows the trends in specific co-morbidities over time

Figures b & c show the un-adjusted trends in disease severity.

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